For the purpose of completeness, a new claim 16 has been added stating that the metabolites are used at a purity of at least 90%. This is consistent with the purity stated in U.S. Patent 5,846,944 previously referred to at page 1, line 22 and now incorporated into this application by reference. A new independent claim 15 has also been added which is directed to the treatment of a specific group of diseases or conditions. Claim 14 has been deleted.

The Examiner has rejected claims 1-3 and 14 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 5, 1-7 and 12 of U.S. Patent No. 5,846,944. While there are arguments for inventive distinction in the present application over the '944 patent, for the sake of advancing the prosecution Applicant has elected to file a terminal disclaimer which has been signed by Applicant's agent. The filing of this terminal disclaimer overcomes the rejection of claims 1-3 and 14 based on U.S. Patent 5,846,944.

The Examiner has also rejected claims 1 and 14 as being anticipated by Clark et al. U.S. Patent 5,837,256. As the Examiner points out, this patent discloses a method of treatment of lupus nephritis which comprises administering to a patient an effective amount of secoisolariciresinol (SECO) or secoisolariciresinol diglucoside (SDG) in substantially pure form.

Claim 14 has been removed from the application, leaving only claim 1 at issue. Claim 15 is an independent claim which comprises all of claims 2-13, while excluding claim 1. Since no objection was raised as to any of claims 2-13, all of claims 2-13 and 15 should be now clearly allowable.

With regard to claim 1, it will be noted that all of the examples of U.S. Patent 5,837,256 show the administration only of SDG and none shows the administration of secoisolariciresinol (SECO) itself. Figure 1 of the patent shows that when SDG is administered, the urine contains secoisolariciresinol (SECO) as well as enterolactone (EL) and enterodiol (ED), but with the ED and EL only in trace amounts.

The present inventor has found that when one or more of the metabolites SECO, ED or EL is administered to a subject, they exhibit excellent antioxidant activity, this activity being about 2-4 times the corresponding activity of SDG.

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It is respectfully submitted that it would not have been obvious from the teaching of the '256 patent that SECO, ED and EL would singly or together be highly effective as an antioxidant as claimed in claim 1. The '256 patent does not consider the question of antioxidant activities and, in particular, does not consider the specific diseases or conditions set out in the claims of this application.

Favourable reconsideration of this application as now amended is respectfully requested.

Respectfully Submitted,
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October 5, 2001

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ANTIOXIDANT ACTIVITY IN SDG METABOLITES

Cross-Reference to Related Application

This application claims the benefit of U.S. Provisional Application No. 60/141,254, filed June 30, 1999.

Background of the Invention

This invention relates to a method for the use of metabolites of secoisolariciresinol diglucoside (SDG) for the treatment of diseases or conditions requiring administration of an antioxidant. These metabolites include secoisolariciresinol (SECO), enterodiol (ED) and enterolactone (EL).

Reactive oxygen species, which include superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (•OH) and singlet oxygen ($^1O_2$), have been implicated in the pathophysiology of numerous diseases, including hypercholesterolemic atherosclerosis, diabetes mellitus, ischemic/reperfusion injury, volume or pressure overload heart failure, hemorrhagic shock, endotoxic shock, ageing, inflammatory bowel disease (Crohn's disease, ulcerative colitis), Parkinson's disease, rheumatoid arthritis and stroke.

Antioxidants such as vitamin E, secoisolariciresinol diglucoside (SDG), probucol, vitamin C, superoxide dismutase, catalase, sulphasalazine, and various other drugs without antioxidant activity, have been shown to be effective to a varying degree in the diseases referred to above. These drugs, with the exception of vitamin C and E and SDG, are expensive and have adverse side effects.

As described in Prasad, U.S. Patent 5,846,944, [incorporated herein by reference,] SDG, isolated from flaxseed, has been shown to be effective in lowering cholesterol, and in reducing the development of atherosclerosis in hypercholesterolemic rabbits. It is also effective in reducing the incidence of diabetes mellitus and preventing endotoxic shock.

Summary of the Invention

Reactive oxygen species are known to be involved in the pathophysiology of ageing and numerous diseases, such as hypercholesterolemic atherosclerosis, type I and

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1. A method of treatment of a disease or a condition requiring the administration of an antioxidant, which comprises administering to a patient an effective amount of a secoisolariciresinol diglucoside (SDG) metabolite selected from the group consisting of secoisolariciresinol (SECO) [in a substantially pure form], enterodiol (ED) [in a substantially pure form], and enterolactone (EL) [in a substantially pure form].
2. A method according to claim [1] 15 wherein said disease is hypercholesterolemic atherosclerosis.
3. A method according to claim [1] 15 wherein said disease is diabetes type I or type II.
4. A method according to claim [1] 15 wherein said condition is ischemic heart disease.
5. A method according to claim [1] 15 wherein said condition is volume or pressure overload heart failure.
6. A method according to claim [1] 15 wherein said condition is the prevention of myocardial injury during open heart surgery.
7. A method according to claim [1] 15 wherein said condition is the prevention of restenosis following persutaneous transluminal coronary angioplasty (PTCA).
8. A method according to claim [1] 15 wherein said condition is hemorrhagic or endotoxic shock.
9. A method according to claim [1] 15 wherein said condition is ageing.
10. A method according to claim [1] 15 wherein said disease is inflammatory bowel disease (Crohn's disease, ulcerative colitis).
11. A method according to claim [1] 15 wherein said disease is Parkinson's disease.
12. A method according to claim [1] 15 wherein said disease is rheumatoid arthritis.
13. A method according to claim [1] 15 wherein said disease is stroke.

[14. A method according to claim [1] 15 wherein secoisolariciresinol diglucoside (SDG) is obtained from flaxseed, and said metabolite is obtained from SDG.]

-- 15. A method of treatment of a disease or a condition selected from the group consisting of hypercholesterolemic atherosclerosis, diabetes type I or type II, ischemic heart disease, volume or pressure overload heart failure, prevention of myocardial injury during open heart surgery, prevention of restenosis following persutaneous transluminal coronary angioplasty (PTCA), hemorrhagic or endotoxic shock, ageing, inflammatory bowel disease, Parkinson's disease, rheumatoid arthritis and stroke, which comprises administering to a patient an effective amount of a

secoisolariciresinol diglucoside (SDG) metabolite selected from the group consisting of secoisolariciresinol (SECO) enterodiol (ED) and enterolactone (EL). --

-- 16. A method according to claim 15 wherein the metabolites are used at a purity of at least 90%. --

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